REMARKS

In the Office Action, the specification and claims 29-31, 37 and 42 are objected; claims 1-44 are rejected under 35 U.S.C. § 112, second paragraph; claims 1-44 are rejected under 35 U.S.C. § 112, first paragraph; claims 1, 3-7, 14, 28-34, 40 and 42-44 are rejected under 35 U.S.C. § 102; and claims 1-7, 20, 22, 28-30 and 32-44 are rejected under 35 U.S.C. § 103. The specification has been amended; and claims 24, 28-31, 37 and 42 have been amended. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with Markings to Show Changes Made**." Applicants respectfully submit that the rejections have been overcome and/or are improper in view of the amendments and/or for the reasons set forth below.

In the Office Action, the specification and claims 29-31, 37 and 42 have been objected as previously discussed. In response, the specification has been amended to address the informalities asserted by the Patent Office except regarding the alleged inconsistency of the terms "group A" and "group 1" as disclosed on page 9 of the specification. With respect to this objection, Applicants believe that the use of such terms as disclosed therein would be clear to one skilled in the art.

Indeed, group A relates to one group of rats that is fed an enteral formula based upon acid whey supplemented with 5% cellulose as disclosed in Example 1 on page 9 of the specification. A second group of rats is identified as group 1 wherein this group is fed a freeze-dried enteral formula based upon sweet whey supplemented with 5% cellulose as further disclosed in Example 1. Further, the threonine content in the mucosa of the rats in both group 1 and group A were measured and compared as identified in the results section of Example 1 on page 10 of the specification. In view of same, Applicants believe that the terms "group A" and "group 1" are clearly defined and, thus should be readily understood by one skilled in the art viewing same. Therefore, Applicants do not believe that further amendments to the specification are required with respect to this alleged objection.

The Patent Office has also objected to claims 29-31, 37 and 42. In response, these claims have been amended to address the objection. Applicants note for the record that the changes made to claims 29-31, 37 and 42 were made for clarification purposes and thus do not have a narrowing effect on the scope of the claimed subject matter. Further, Applicants do not intend to disclaim any subject matter as a result of the amendments.

Accordingly, Applicants believe that the specification and claim objections should be withdrawn.

In the Office Action, claims 1-44 are rejected under 35 U.S.C. § 112, second paragraph. Of course, the standard for determining whether the definitiveness requirement pursuant to 35 U.S.C. § 112, ¶ 2 has been met is "whether those skilled in the art would understand what is claimed when the claim is read in light of the Specification." *Orthokinetics Inc. v. Safety Travel Chairs Inc,* 1 U.S.P.Q. 2d 1081-1088 (Fed. Cir. 1986). "If the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the Courts can demand no more." *North American Vaccine Inc. v American Cyanamid Co.,* 28 U.S.P.Q. 2d 1333, 1339 (Fed. Cir. 1993). In this regard, "[p]atent law allows the inventor to be his own lexicographer ... [T]he specification aids in ascertaining the scope and meaning of the language employed in the claims inasmuch as words must be used in the same way in both the claims and the specification." *United States v. Teletronics, Inc.,* 8 U.S.P.Q. 2d 1217, 1220 (Fed. Cir. 1988). Applicants believe that the rejections under 35 U.S.C. § 112, ¶ 2 has been overcome in view of the amendments and/or for the reasons set forth below.

With respect to the rejection of claims 24 and 28 as indicated on page 4 of the Office Action, Applicants have amended the claims and thus believe that the rejections in view of same has been overcome. Applicants note for the record that these amendments were made for clarification purposes and thus do not have a narrowing effect on the scope of the claimed subject matter. Further, Applicants do not intend to disclaim any subject matter as a result of these amendments.

With respect to the rejection of claim 1 (See, Office Action, page 3), Applicants believe that this claim is clearly defined in meaning and scope as supported in the specification. Claim 1 recites a method of treating a disease state characterized by alterations to the mucin levels in a patient. The method includes enterally administering to the patient a nutritional composition which has a protein source that includes amino acids wherein threonine includes at least 5.5% by weight of the amino acids. As disclosed in the specification on page 1 at lines 18-21, mucins are glycoproteins which are a primary component of the viscoelastic gel, or mucus, which covers most of the mucosal surfaces of the gastrointestinal tract and lungs. They are continuously secreted from the surfaces of the lung and gastrointestinal tract. The mucus acts to protect the

epithelial cells of the gastrointestinal tract and lungs from toxins. See, specification, page 1, lines 26-27. However, many disease states are characterized by alterations in the mucus composition. For example, histochemical studies have demonstrated well characterized abnormalities in mucins during malignancy and due to other infection as further disclosed in the specification on page 2 at lines 3-8.

With respect to the claim term "a protein source including amino acid", the specification discloses that the protein source may be in the form of intact protein, hydrolyzed protein, or mixtures thereof. Further, if desired, the protein source may be in the form of free amino acids. The protein source may also be in the form of mixtures of intact protein or hydrolyzed protein with free amino acids. See, specification, page 5, lines 15-21. Moreover, the protein source may be naturally enriched in threonine or by supplementing other protein sources with threonine. See, specification, page 5, lines 25-26.

With respect to the claim term "enterally administering", indeed, enteral feeding is generally recognized to mean using the gastrointestinal tract for the delivery of nutrients. This can include eating food, consuming oral supplements, tube feeding, and the like. Therefore, Applicants believe that one skilled in the art would clearly understand the meaning and scope of claim 1 as presently defined and as further supported in the specification as discussed above.

With respect to claim 2 (See, Office Action, pages 2-3), Applicants believe that the claim term "by weight of the amino acids" is clearly definable. As previously discussed, the amino acids can be derived from intact proteins, hydrolyzed proteins, free amino acids and mixtures thereof as supported in the specification. Further, the threonine content can be defined as a percentage by weight of the protein source. See, specification, page 9, lines 29-31.

With respect to the claim term "about 30% to about 80%" as defined, for example, in claim 7 (See, Office Action, 4), Applicants believe that the use of the term "about" is proper. As disclosed in the specification on page 6 at lines 21-24, the lipid source may include a mixture of medium chain triglycerides and long chain triglycerides. Preferably, the lipid source includes at least 30% to about 80% by weight of medium chain triglycerides. Clearly, one skilled in the art viewing same would not consider that the term "about" would render the claimed medium chain triglycerides range ambiguous.

With respect to the claim term "maintaining the synthesis of mucins in a patient" (See, Office Action, page 4), Applicants believe that this claim term is clear in scope and meaning.

Clearly, one skilled in the art would understand that the term "maintaining" means to keep mucin synthesis at a relatively constant and desirable level even in the presence of a disease state that is known to impair mucin reduction as disclosed in the specification. In this regard, Applicants have discovered that threonine supplementation can be an efficient and effective nutritional intervention to stimulate or to restore the mucoprotein synthesis rate, and thus to facilitate improved epithelial cell protection. See, specification, page 13, lines 28-30. Further, the claim term "a patient" can include patients suffering from, or at risk of, impaired or reduced mucin production as disclosed in the specification on page 7 at lines 14-15. Therefore, Applicants believe one skilled in the art viewing same would consider that the claim term "maintaining the synthesis of mucins in a patient" is not indefinite in meaning.

Lastly, the Patent Office asserts that the recitation "a daily recommended amount of threonine" as defined, for example, in claim 32 (See, Office Action, pages 4-5), is ambiguous in meaning. Indeed, the specification discloses that the amount of threonine to be added can be based on the recommended daily dosages or requirement for threonine. For example, the amount of threonine added to the diet can include at least 30% of the recommended daily amount, preferably at least 60%, and most preferably at least 100% of this amount. See, specification, page 8, at lines 16-19. One skilled in the art would recognize in view of same that although the recommended daily dosages may vary between subjects this does not render the claims indefinite as the amount of threonine is based on the recommended dosage or requirement for threonine, such as a percentage of the recommended daily amount as discussed above.

Based on at least these noted reasons, Applicants believe that claims 1-44 comply with 35 U.S.C. § 112, second paragraph. Therefore, Applicants respectfully request that this rejection be withdrawn.

In the Office Action, claims 1-44 are rejected under 35 U.S.C. § 112, first paragraph. In general, the Patent Office argues that undue experimentation is required to practice the invention as claimed. Applicants believe that this objection is not proper as detailed below.

At the outset, Applicants respectfully submit that the enablement rejection appears to be at odds with the anticipation and obviousness rejections. In this regard, the Patent Office asserts that the art is to unpredictable for the claims to be enabled but then argues that the claimed invention would be anticipated or obvious in view of the cited art. If the claimed invention is too unpredictable to be enabled, how can the claimed invention be anticipated or obvious? Surely, if

the Patent Office can assert anticipation and/or obviousness rejections in view of Applicants disclosure of the claimed invention, then the claimed invention must be enabled.

In any event, Applicants believe that the claimed invention satisfies the enablement requirement. Of the claims at issue, claims 1, 8, 14, 20, 24, 28, 32, 35 and 40 are the sole the independent claims. Claim 1 relates to a method of treating a disease state characterized by alterations to the mucin levels in a patient; claim 8 relates to a method of maintaining the synthesis of mucins in a patient; claim 14 relates to a method of maintaining the synthesis of mucins in a patient; claim 20 relates to treating a disease state characterized by alterations to the mucin levels in a patient; claim 24 relates to a method for maintaining the synthesis of mucins in a patient; claim 28 relates to a method for increasing the synthesis of mucins in a patient; claim 32 relates to a method for increasing the synthesis of mucins in a patient; claim 35 relates to a method of treating intestinal inflammation in a patient; and claim 40 relates to a method of treating intestinal bacterial infection in a patient.

Each of the independent claims requires administering a therapeutically effective amount of threonine to the patient, such as a nutritional composition that includes a protein source and a sufficient amount of threonine. Applicants have discovered that administering threonine to a patient can maintain, improve or increase the synthesis of mucins in the patient and thus can have a beneficial effect on the treatment of a variety of disease states that are known to impair mucin production. For example, claim 1 recites enterally administering a nutritional composition with a protein source wherein threonine includes at least 5.5% by weight of the amino acids; claims 20 and 24 recite enterally administering to the patient a nutritional composition with a protein source wherein threonine includes at least 7.4% by weight of the amino acids; and claim 32 recites that threonine is administered in a protein source that contains at least 30% of a daily recommended amount of threonine.

Applicants have conducted a number of experiments to demonstrate the beneficial effects of the claimed invention. The experiments provide examples of nutritional compositions that include threonine according to an embodiment of the claimed invention. Thus, Applicants believe that one skilled in the art viewing same would be able to make the nutritional compositions and further be able to administer same to a patient as required by the claimed invention. Indeed, the claims recite administering a therapeutically effective amount of threonine to a patient to maintain, improve or increase the synthesis rate of mucins in the patient,

thus allowing treatment of certain disease states, such as intestinal inflammation (claim 35) or intestinal bacterial infection (claim 40), as required by the claimed invention.

Contrary to the Patent Office's position, Applicants believe that the specification provides sufficient guidance such that one skilled in the art should be able to make and administer the nutritional compositions that contain threonine as claimed without excessive experimentation. For example, the compositional make-up of an isotonic liquid diet according to an embodiment of the claimed invention is disclosed in Example 2. In particular, the diet includes a hydrolyzed sweet whey protein source and threonine at about 7.4% by weight of the protein source. The diet is available from Nestle Clinical Nutrition under the trademark PEPTAMEN®. See, specification, pages 10-11. Each patient in the study was fed the PEPTAMEN® product as the sole source of nutrition for a period of eight weeks.

Administration of the nutritional composition was under the supervision of a dietitian and was effected orally, or by a nasogastric tube, as desired by the patient. See, specification beginning on page 11 at line 16 to page 12 at line 1. This study demonstrated that mucus conditions in all patients improved after administering the nutritional composition to the patients as described in Example 2. This resulted in the remission of Crohn's disease in most of the ten patients who were diagnosed as suffering from Crohn's disease. See, specification page 12, lines 5-8.

Further, Applicants have demonstrated with both *in vitro* and *in vivo* studies that threonine supplementation can be an effective and efficient nutritional strategy to increase or restore the mucoprotrein synthesis rate, and thus to ensure a better epithelial cell protection. See, specification, Examples 3 and 4, pages 12-16. Again, the claimed invention recites administering a therapeutically effective amount of threonine to a patient to maintain, improve or increase the synthesis rate of mucins in the patient. This can facilitate treatment of disease states that are known to impair mucin production as previously discussed. In view of same, Applicants believe that one skilled in the art would be able to make and/or use the claimed invention without undue experimentation.

The Patent Office has also asserted that the claims directed to unlimited threonine contents, such as threonine including at least 5.5% by weight of the amino acids (claims 1, 8, 15 and 38), would arguably render the disclosure unpredictable. Contrary to the Patent Office's position, Applicants believe that the amount of threonine as claimed is sufficiently described in

the specification such that one skilled in the art would readily be able to make and use the claimed invention in view of same. Again, the examples disclosed in the specification should provide one skilled in the art with a sufficient level of understanding, information and/or guidance to make and/or use the claimed invention. As previously discussed, Example 2 details the feeding of a nutritional composition that includes threonine at about 7.4% by weight of the protein source according to an embodiment of the claimed invention. This effectively resulted in improved mucus conditions and in the remission of Crohn's disease as previously discussed. Thus, the disclosure, such as Example 2, provides a template from which one skilled in the art can readily practice the claimed invention without undue experimentation.

Based on at least these noted reasons, Applicants believe that claims 1-44 comply with 35 U.S.C. § 112, first paragraph. Accordingly, Applicants believe that this rejection should be withdrawn.

In the Office Action, claims 1; 3-7, 14, 28-34, 40 and 42-44 are rejected under 35 U.S.C. § 102. More specifically, claims 14 and 28-34 are rejected in view of *Bertolo et al.*; and claims 1, 3-7, 40 and 42-44 are rejected in view of U.S. Patent No. 6,468,987 ("*Demichele*"). Applicants believe that the rejections are improper set forth in detail below.

With respect to the rejection in view of *Bertolo et al.*, claims 14, 28 and 32 are the sole independent claims at issue. Claim 14 recites a method for maintaining the synthesis of mucins in a patient including enterally administering to the patient a nutritional composition which includes, in part, a protein source that contains a therapeutically effective amount of threonine. Claim 28 recites a method of increasing the synthesis of mucins including supplementing a diet of a patient by adding a therapeutically effective amount of threonine to the diet. Claim 32 recites a method for increasing the synthesis of mucins in a patient including administering to the patient a nutritional composition which has a protein source that contains at least 30% of a daily recommended amount of threonine. As previously discussed, Applicants have discovered that mucin synthesis can be maintained, improved or increased by administering a therapeutically effective amount of threonine to a patient suffering from or at risk of impaired or reduced mucin production. This can facilitate the treatment of a disease state that can alter the mucin levels in the patient.

In contrast, Applicants believe that *Bertolo et al.* fails to disclose or arguably suggest at least a number of features as required by the claimed invention. Contrary to the Patent Office's

position, nowhere does this reference disclose or arguably suggest that mucin synthesis can be maintained, improved or increased by administering a therapeutically effective amount of threonine to a patient or supplementing a diet with same as required by the claimed invention. Indeed, this reference merely relates to employing an experimental procedure to evaluate and assess the threonine requirement in a neonatal piglet model receiving total parenteral nutrition. See, *Bertolo et al.*, pages 1752-1753. In this regard, the parenteral threonine requirement was determined by examining the effects of varying dietary threonine intakes on phenylalanine oxidation. See, *Bertolo et al.*, Abstract, page 1752. Based on at least these reasons, Applicants believe that *Bertolo et al.* is deficient with respect to the claimed invention.

Further, the Patent Office alleges that claims 1, 3-7, 40, 42-44 are anticipated by *Demichele* as previously discussed. Of these pending claims at issue, claims 1 and 40 are the sole independent claims. Claim 1 recites a method of treating a disease state characterized by alterations to the mucins levels in a patient including enterally administering to the patient a nutritional composition with a protein source that includes amino acids wherein threonine includes at least 5.5% by weight of the amino acids. Claim 40 recites a method of treating intestinal bacterial infection in a patient including administering a nutritional composition to the patient wherein the nutritional composition contains a therapeutically effective amount of threonine. As previously discussed, Applicants have discovered that mucin production can be restored or stimulated by administering a therapeutically effective amount of threonine to a patient thus facilitating treatment of a disease state that can impair or reduce mucin production.

In contrast, Applicants believe that this reference is defective with respect to the claimed invention. At the outset, nowhere does this reference disclose or arguably suggest that a therapeutically effective amount of threonine can be administered to the patient in order to treat disease in the patient that can alter mucin levels. Indeed, nowhere does this reference articulate a connection between the administration of a therapeutically effective amount of threonine to a patient and its beneficial effects on mucin production, thus leading to the treatment of a disease state that can impair or reduce mucin production in the patient as required by the claimed invention. Contrary to the Patent Office's position, the mere disclosure in *Demichele* that a nutritional product can include 75% whey protein concentrate is insufficient in detail and specificity to suggest same.

Based on at least these noted reasons, Applicants believe that *Bertolo et al.* or *Demichele* fail to disclose or arguably suggest the claimed invention. Therefore, Applicants believe that these references fail to anticipate the claimed invention.

Accordingly, Applicants respectfully request that the anticipation rejections be withdrawn.

In the Office Action, claims 1-7, 20, 22, 28-30 and 32-44 are rejected under 35 U.S.C. § 103 in view of *Hennebicq-reig, et al.* in combination with *Demichele*, U.S. Patent No. 5,728,678 ("*Trimbo*") and U.S. Patent No. 6,187,558 ("*Granados*"). The Patent Office primarily relies on *Hennebicq-reig, et al.* and thus relies on the combined teachings of the remaining cited art to remedy the deficiencies of *Hennebicq-reig, et al.*.

Applicants believe that the cited art fails to disclose or suggest at least a number of features of the claimed invention. With respect to the primary reference, its focus relates to the effect of GalNacα-O-benzyl on mucin synthesis and secretion. Indeed nowhere does this suggest that mucin production can be maintained, increased or improved by administering a therapeutically effective amount of threonine to a patient, thus leading to the treatment of a disease state that can impair or reduce mucin production as required by the claimed invention. Further, nowhere does this reference disclose or suggest the specific amounts of threonine that can be administered, such as threonine that includes at least 5.5% by weight of the amino acids of the protein source (claim 1), as required by the claimed invention. Therefore, the primary reference is clearly deficient with respect to the claimed invention.

Further, Applicants do not believe that the remaining cited art, even if combinable, can remedy the deficiencies of the primary reference. For example, the *Trimbo* reference relates to composition for providing nutrition to a renal failure patient. Foremost, this relates to a different application than as required by the claimed invention. As previously discussed, the claimed invention requires administering a therapeutically effective amount of threonine to a patient in order to increase or maintain mucin production and thus further facilitating the treatment of a disease state that is capable of altering mucin levels in the patient. Based on at least this difference, Applicants question whether this reference is combinable with the other art in the first place.

As previously discussed, the *Demichele* reference fails to disclose or suggest a connection between mucin production and the administration of the therapeutically effective

amount of threonine to a patient. Further, Applicants believe that this reference is deficient with respect to the specific amounts of threonine that can be effectively administered, such as at least 5.5% by weight, 6% by weight, let alone 7.4% by weight of the amino acids of the protein source in the nutritional composition as required by the claimed invention.

Moreover, the Patent Office merely relies on *Granados* for its purported teachings relating to the protective function of mucin in intestinal mucosal layer, that mucin plays an active role in preventing bacterial infection, and that mucin is rich in threonine. Yet, this does not suggest that the administration of an effective amount of threonine to a patient can maintain, improve or increase mucin production in the patient and further leading to the treatment of disease that can alter mucin levels in the patient.

What the Patent Office appears to have done is to rely on hindsight reasoning to justify the obviousness position. Of course, this is clearly improper. Again, the primary reference is deficient with respect to any mention of administering threonine, let alone at a specified amount, to stimulate or restore mucin production and further facilitate the treatment of disease that can alter mucin production as required by the claimed invention. As previously discussed, the remaining cited art, even if combinable, fails to provide a sufficient level of teaching to remedy the deficiencies of the primary reference. Therefore, Applicants believe that one skilled in the art viewing same would not be inclined to modify the primary reference to arrive at the claimed invention.

Based on at least these noted reasons, Applicants believe that the cited art fails to disclose or suggest at least a number of features of the claimed invention. Therefore, Applicants respectfully submit that the cited art, even if combinable, fails to render obvious the claimed invention. Accordingly, Applicants respectfully request that the obviousness rejection be withdrawn.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please substitute the paragraph beginning on page 5 at line 12 with the following rewritten paragraph:

The invention is based on the finding that enterally administering nutritional composition which contains a protein source enriched in threonine has a beneficial effect on the synthesis of mucins. The protein source may be any suitable source of amino acids that is enriched in threonine. For example, the protein source may be milk protein, egg white, caseino-glyco -macropeptide, whey protein, casein protein, soy protein, rice protein, pea protein or oat protein, or mixtures of these proteins. Also, the protein source may be in the form of intact protein, hydrolyzed protein, or mixtures thereof. Further, if desired, the protein source may be in the form of free amino acids. In an embodiment, the protein may be in the form of mixtures of intact protein or hydrolyzed protein, with free amino acids.

Please substitute the paragraph beginning on page 12 at line 27 with the following rewritten paragraph:

After 24 hours of metabolic labeling, the culture medium of cells was removed. Cells were washed twice with 10 ml of 1 X phosphate buffer solution (PBS) and recovered using a rubber scraper. Cells were homogenized in 0.05M Tris/HCl buffer pH 7.50 using a polytron at a low setting (6.000 rpm, 30 sec, 4°C). An aliquot of each homogenate was removed for the measurement of the specific radioactivity of the intracellular free threonine considered as the precursor pool. Mucoproteins were purified from the cell homogenates by a size exclusion chromatography after a partial enzymatic digestion of non-highly glycosylated and thus protected proteins. Purified mucins were hydrolyzed with 6M HCl (24h at 100°C), and their amino acid composition was determined by HPLC. The outlet of the UV detector was connected to a radioactive detector (Radiomatic 500TR, Packard) to measure the ^{3}H-threonine incorporated in mucoproteins. The fractional synthesis rate (FSR) of mucoproteins was calculated and expressed in percent/day (%/d): (FSR = (Specific radioactivity of mucoprotein bound threonine/Specific radioactivity of intracellular free threonine) * 100).

Please substitute the paragraph beginning on page 14 at line 19 with the following rewritten paragraph:

Rat mucosal samples were gently homogenized in 0.05M Tris/HCl buffer pH 7.50 using a polytron at a low setting (6~~,~~000 rpm, 30 sec, 4°C). An aliquot of each sample homogenate was used to measure the 1-^{13}C-Valine enrichment in the intracellular pool that was considered as ^{13}C-enrichment of the precursor pool. Thereafter, mucoproteins were purified as described previously for the *in vitro* experiment. 1-^{13}C-Valine enrichments in mucoproteins were measured by mass spectrometry.

In the Claims:

Claims 24, 28-31, 37 and 42 have been amended as follows:

24. (Amended) A method for maintaining the synthesis of mucins in a patient, the method comprising enterally administering to the patient a nutritional composition which has a protein source including amino acids wherein threonine comprises at least 7.4% by weight of the amino acids.

28. (Amended) A method for increasing the synthesis of mucins in a patient, the method comprising supplementing a diet of ~~a~~the patient by adding a therapeutically effective amount of threonine to the diet.

29. (Amended) The method of claim 28 wherein the amount of threonine is at least 0.2 mM.

30. (Amended) The method of claim 28 wherein the amount of threonine is at least 0.8 mM.

31. (Amended) The method of claim 22 wherein the amount of threonine ranges from about 0.2 mM to about 0.8 mM.

37. (Amended) The method of claim 36 wherein the nutritional supplement contains threonine in an amount of at least 0.2 mM.

42. (Amended) The method of claim 41 wherein the nutritional supplement contains threonine in an amount of at least 0.2 mM.